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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/531,626 | 03/30/2006 | Jennifer Ruth Gamble | 650063.402USPC | 8192 |

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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

| EXAMINER | |
|---|---|
| SGAGIAS, MAGDALENE K | |
| ART UNIT | PAPER NUMBER |
| 1632 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/531,626 | GAMBLE ET AL. | |
| | Examiner | Art Unit | |
| | Magdalene K. Sgagias | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,8,10,13,15,21-25 and 43* is/are pending in the application.

4a) Of the above claim(s) *21-24 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8,10,13,15,25 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's arguments filed 11/05/07 have been fully considered but they are not persuasive. The amendment has been entered. Claims 1-6, 8, 10, 13, 15, 21-25, 43 are pending. Claims 7, 9, 11-12, 14, 16-20, 27-42 are canceled. Claims 21-24, 26 are withdrawn. Claims 1-6, 8, 10, 13, 15, 25, 43 are under consideration.

The Examiner inadvertently included the non-elected claim 26 in the previous office action mailed 5/3/07. Therefore, claim 26 is currently withdrawn from consideration.

### *Specification*

The disclosure's objection to because it contains an embedded hyperlink is withdrawn.

### *Claim Rejections - 35 USC § 112, 1st paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, 10, 13, 15, 25, 43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a nucleic acid molecule encoding a sphingosine kinase functional fragment, or homologue thereof. The claims do not require that the produced protein possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus,

the claim is drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, there is no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification discusses "Derivatives"

of the molecules herein described (for example sphingosine kinase or other proteinaceous or non-proteinaceous agents) include fragments, parts, portions or variants from either natural or non-natural sources [0101]. The specification also discusses parts or fragments include, for example, active regions of the molecule and derivatives may be derived from insertion, deletion or substitution of amino acids [0101]. The genes coding for a sphingosine kinase functional fragment or homologue thereof encompassed within the genus of genes coding for a sphingosine kinase protein, functional fragments or homologs thereof, have not been disclosed. There is no evidence on the record where the specification teaches any characteristics of a sphingosine kinase functional fragment or homolog thereof that would distinguish it from a non-natural variant constructed by the hand of man.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by a member of the genus of SK capable of modulating endothelial cell functional characteristics in vivo. The specification provides evidence of possession for overexpression of sphingosine kinase by introducing an adenovirus containing sphingosine kinase enhances cell survival of human umbilical vein endothelial cells (HUVEC) in vitro (example 1). The specification also provides evidence for overexpression of sphingosine kinase alters adhesion molecule expression in HUVEC, enhances neutrophil adhesion to endothelial cells and promotes tube formation or the endothelial cells arrange into a capillary like network (tubes) in vitro, (example 2). Therefore, Applicant was not in possession of the genus of sphingosine kinase functional fragment or homolog thereof, as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

Applicants argue that information which is well known in the art need not be described in detail in the specification. Applicants argue that "homologs thereof" is clearly defined on p. 26, lines 23-28 of the as-filed specification as a sphingosine kinase molecule which is derived from a species other than that which is being treated by the method of the invention. Applicants argue that the mouse, rat, monkey, S. cerevisiae, S. pombe, A. thaliana, and O. saliva sphingosine kinase sequences were known prior to the effective filing date of the instant application, and thus, in possession of the skilled artisan and there is extremely high degree of conservation in important regions necessary for sphingosine kinase activity between such diverse species as human to rice. Thus, not only were many of the homologues for sphingosine kinase known, but the homologues all possess an extremely high degree of sequence identity in the nucleotide binding domain. Applicants argue the skilled artisan would easily recognize functional fragments and homologues of sphingosine kinases as these properties have been documented in the art and the skilled artisan would how to perform assays for sphingosine kinase activity as such assays were well known in the art at the time of filing the instant application.

These arguments are not persuasive because the claims encompass fragments of nucleic acids or homologues thereof, that encode fragments of homologues thereof of sphingosine kinase. These claims are extremely broad since insufficient guidance is provided as to which of the plethora of fragments of nucleic acids encode sphingosine kinase polypeptides which will retain the characteristics of a functional sphingosine kinase. While the claims are directed to fragment of nucleic acid encoding sphingosine kinase Applicants do not disclose any actual examples or prophetic examples on expected performance parameters of any of possible encoded fragments of a functional sphingosine kinase. The specification discusses that parts or fragments include, for example, active regions of the molecule and

derivatives may be derived from insertion, deletion or substitution of amino acids [0101]. It is known in the art that even a single nucleic acid change or difference in the nucleic acid sequence of a protein can have dramatic effects on the protein's function. Second a skilled artisan having knowledge of the mouse, rat, monkey, S. cerevisiae, S. pombe, A. thaliana, and O. saliva sphingosine kinase sequences and that the sphingosine kinase homologues all possess an extremely high degree of sequence identity in the nucleotide binding domain and knowing how to generate fragments parts or fragments for example, active regions of the molecule and derivatives from insertion, deletion or substitution of amino acids of the sphingosine kinase molecule will not be able to recognize that the Applicant was in possession of the claimed invention because each fragment having distinct sequence structure elicit distinct functional characteristics in the claimed sphingosine kinase molecule. The broadly claimed fragments fail to uniquely identify the structural and functional characteristics of the claimed sphingosine kinase.

While the specification discloses that the sphingosine kinase homologues all possess an extremely high degree of sequence identity in the nucleotide binding domain and knowing how to generate fragments parts or fragments for example, active regions of the molecule and derivatives from insertion, deletion or substitution of amino acids of the sphingosine kinase molecule in the absence of teachings of he complete structure and function of the fragments of the gene as well as the sphingosine kinase protein encoded by the fragment of the gene, an artisan would not know what to mutate and where to mutate in the gene. The claimed invention is not adequately described if the claims require essential or critical functional fragment or homologues of sphingosine kinase nucleic acid sequences which are not adequately described by the specification and which are not convention in the art at the time of filing. Possession may be shown by actual reduction to practice, or by describing the invention with sufficient relevant

identifying characteristics as it relates to the claimed invention as a whole such that one of skill in the art would recognize that Applicants had possession of the invention. The specification does not provide any teachings whether such fragment would retain the function of sphingosine kinase.

Claims 1-6, 8, 10, 13, 15, 25, 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for overexpression of sphingosine kinase by introducing into mammalian endothelial cells a nucleic acid encoding sphingosine kinase resulting in enhancing cell survival, altering adhesion molecule expression and enhancing neutrophil adhesion to endothelial cells and promote tube formation or the endothelial cells arrange into capillary like network in vitro, does not reasonably provide enablement for modulating one or more mammalian endothelial cell functional characteristics by way of the claimed methods in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue that that the presently claimed invention has been reduced to practice in vitro, namely the transmission of an adenoviral-based transgene in order to over-express a functional sphingosine kinase molecule, which modulates endothelial cell characteristics (see Examples 1 and 2). Applicants argue that the use of in vitro experiments to establish in vivo events is, in principle, a valid methodology.

These arguments are not persuasive because the in vitro examples do not provide guidance for the in vivo delivery of a nucleic acid molecule encoding sphingosine kinase or functional fragments or homologues thereof such that the endothelial cell functional characteristics are modulated. Cell culture data, of the HUVEC cells which is an in vitro system,

is not directly correlatable to the modulation of endothelial cell characteristics in vivo or to the treatment and/or prophylaxis of a condition characterized by aberrant endothelial cell function in a mammal. The delivery of a nucleic acid to tissue culture cells does not provide guidance for overcoming the obstacles of in vivo delivery because the nucleic acid does not have to cross through the complex organization of organs and tissues. Cell cultures do not mimic in vivo organs in that there is no three-dimensional structure, blood vessels, connective tissue, through which the nucleic acid would be required to cross through in vivo.

Applicants argue that the references Lee et al. (Lee et al., Coronary Artery Disease, Vol. 16, No. 7, pp. 451- 456, 2005) and Duan et al., (Duan et al., Human Gene Therapy, 18:000-000, pp. 1-10, Nov. 2007) as post-filing evidence that adenoviral vectors containing sphingosine kinase were effectively utilized in rabbit and rat animal models, respectively. Applicants argue that the post-filing evidence for reduction to practice of the presently claimed adenoviral system clearly demonstrates that Applicants methods are adequately described to one of skill in the art in order to practice the invention in an in vivo setting. Moreover, both post-filing examples clearly demonstrate the efficacy of transgenic sphingosine kinase in promoting angiogenesis and improving the outcome of ischemic failure models.

These arguments are not persuasive because for example the correlation of the data derived from in vitro studies to in vivo testing of a therapeutic protein, in vitro studies of the protein's function at the cellular level involve interactions with other macromolecules, precluding studies of physiological for example metabolic pathways and phenotypic functions for example role in the whole mammal of such protein. In the instant case, the HUVEC cells in vitro preclude the measurements of sphingosine kinase activity in cardiomyocytes in vivo, as in Lee and/or Duan testing of sphingosine kinase therapeutic protein. The in vitro studies of sphingosine kinase's function at the cellular level involve interactions and cues with other molecules that

preclude the estimation of creatine kinase release, or heart morphometry or hemodynamic assays in the whole rat of sphingosine kinase cell functional characteristics as in Lee et al reference. As discussed in the previous office action cell cultures do not mimic organs in that there is no three-dimensional structure, blood vessels, connective tissue through which the vector would need to pass in vivo.The instant specification does not provide any relevant teachings, specific guidance, or working examples for overcoming the limitations of SK gene transfer in vivo resulting in the modulation of endothelia cell in vivo or in the treatment and/or prophylaxis of a disease raised by the state of the art.

Therefore, in view of the lack of guidance in the specification and in view of the teachings in the art at the time of filing regarding sphingosine kinase gene therapy, the skilled artisan would require engaging in an undue amount of experimentation without a predictable degree of success to implement in the invention as claimed.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5, **stand** rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6, 15-20 of U.S. Patent No. 10275,686. Applicants argue that until time the claims are in condition for allowance, Applicants will submit a terminal disclaimer.

Claims 1-2, 5-7, 15 **stand** rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15, 17, 23, of U.S. Patent No. 09/977,217. Applicants argue that until time the claims are in condition for allowance, Applicants will submit a terminal disclaimer.

***Conclusion***

**No claim is allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The

examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
Primary Examiner, Art Unit 1632